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学位論文題名	5-Aminolevulinic acid combined with sodium ferrous ameliorated liver injury in a murine aGvHD model by reducing inflammation responses through PGC-1α activation （5-ALA/SFC の PGC-1α活性化を通じた炎症反応の軽減によるマウス急性移植片対宿主病モデル肝障害に対する改善効果）
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【論文の内容の要旨】

Background: Acute graft-versus-host disease (aGvHD) remains lethal, even after allogeneic hematopoietic stem cell transplantation. Inflammatory responses play an important role in aGvHD. 5-Aminolevulinic acid combined with sodium ferrous citrate (5-ALA/SFC) has been widely reported to have a major effect on the anti-inflammatory response, but these effects in an aGvHD model have never been reported.

Materials and Methods: Male 8-12-week-old C57BL/6NJcl (B6/J, H-2kb) mice as the donor animal and 7-8-week-old C57BL/6NJcl x DBA/2NJcl mice as the recipient were employed. Mice were randomly assigned to two groups: those receiving 5-ALA hydrochloride (100 mg/kg) and SFC (157 mg/kg) daily from days 0 to 7 or 14 as the 5-ALA/SFC-group, and those receiving distilled water as the control group. After 14 days, we measured the expression ofinflammation related cytokines and chemokines in aGvHD mice after 5-ALA/SFC treatment. Serum levels of ALT and AST were commonly used as biochemical indicators of liver injury. In addition, the histopathological analysis of liver tissues was performed.

Results: 5-ALA/SFC ameliorated liver injury in aGvHD and promoted survival in mice. 5-ALA/SFC treatment resulted in decreased expression of pro-inflammatory cytokines

and chemokines whose expressions in liver are normally elevated by aGvHD. Furthermore, 5-ALA/SFC treatment also enhanced PGC-1α expression in liver tissue and HO-1 expression in nonparenchymal cells. These results indicated that the protective effect of 5-ALA/SFC relies on suppressing the inflammatory response phase in the aGvHD model, presumably by inducing HO-1.

Conclusion: This study demonstrated that 5-ALA/SFC could serve as an effective treatment on liver injury via modulating inflammatory responses in the aGVHD mouse. The mechanistically therapeutic effect of 5-ALA/SFC may rely on PGC-1α activation and modulating the liver mRNA expression of the inflammatory related cytokines and chemokines. Thus, this research may offer a novel therapeutic option for aGvHD, and encourage future studies of this promising therapeutic agent for the treatment of aGvHD.

KEYWORDS: 5-aminolevulinic acid, acute graft-versus-host disease, liver injury, inflammatory cytokines, PGC-1α,